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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/576,142	12/06/2006	Thomas Arendt	4121-180	5650
23448	7590	07/31/2008	EXAMINER	
INTELLECTUAL PROPERTY / TECHNOLOGY LAW			MACFARLANE, STACEY NEE	
PO BOX 14329			ART UNIT	PAPER NUMBER
RESEARCH TRIANGLE PARK, NC 27709			1649	
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	10/576,142	ARENDT ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	STACEY MACFARLANE	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

1) Responsive to communication(s) filed on 29 May 2008.

2a) This action is **FINAL**.                            2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

4) Claim(s) 1-13 is/are pending in the application.

4a) Of the above claim(s) 9-13 is/are withdrawn from consideration.

5) Claim(s) \_\_\_\_\_ is/are allowed.

6) Claim(s) 1-8 is/are rejected.

7) Claim(s) \_\_\_\_\_ is/are objected to.

8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All    b) Some \* c) None of:

1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

1) Notice of References Cited (PTO-892)

2) Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) Information Disclosure Statement(s) (PTO/SB/08)  
Paper No(s)/Mail Date 9/5/2006; 12/18/2006.

4) Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_ .

5) Notice of Informal Patent Application

6) Other: \_\_\_\_\_.

## DETAILED ACTION

### ***Election/Restrictions***

1. Applicant's election of Group I and the species CD4+ and CD8+ cells and the PWM stimulation in the reply filed on May 29, 2008 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).
2. Claims 9-13 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on May 29, 2008.
3. Claims 1-8, in so far as they read upon the elected species, will be examined upon their merits.

### ***Claim Rejections - 35 USC § 112***

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.
5. Claims 1-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.
6. Claim 1 is vague and indefinite in its recitation of quantification of "mitogenically stimulated cells ...before and after step (a)". Since step (a) constitutes the active step in which the cells are stimulated it is unclear how the cells can be stimulated cells

*before* this step. It is not clear if Applicant intends to encompass mitogenic stimulation that occurs prior to the active step of (a). Therefore, the metes and bounds of the claim are undeterminable.

7. Claim 1 is further rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: steps leading to a quantification of surface markers before stimulation and steps leading to a determination of the number of cells bearing the surface marker before stimulation. As the claim stands, the method seems to require unstated active steps that precede the first active step, step (a).

8. Claim 5 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: the relationship between the anticoagulative compound and the “stabilization” of the blood sample. It is unclear if the mere contact of the blood sample with the compound results in “stabilization” or if other omitted steps are required. Claim 5 is also indefinite in that it further limits a method by adding steps that precede the active steps of the method and in this way the method of claim 5 can be infringed by a materially different method than that of the parent claim.

9. Claims 2-4 and 6-8 are indefinite because they depend from an indefinite claim(s).

***Claim Rejections - 35 USC § 102***

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 1-4 and 6 are rejected under 35 U.S.C. 102(b) as being anticipated by Neubert et al., *Teratogenesis, Carcinogenesis, and Mutagenesis*, 20:171-193 (2000).

12. Instant claims 1-4 and 6 are drawn to a method of diagnosing Alzheimer's disease or an early stage of or a predisposition for this disease by means of a patient sample, the method comprising the steps of: (a) mitogenic stimulation of the cells in the sample; (b) quantification of the cells before and after stimulation by means of one or more surface markers, the cells bearing the surface markers being separated from the cells bearing no surface markers by means of antibodies directed against the surface markers; (c) determination of the stimulation index as a relationship of the number of cells bearing the surface marker before or after step (a). Dependent claims recite, wherein the cells are lymphocytes; the surface marker is CD69 and wherein the CD69+ cells are further specified with respect to CD4 and CD8; and wherein the cells are stimulated by the instantly-elected pokeweed mitogen (PWM).

13. The Neubert et al. prior art teaches a method comprising the active steps of stimulating lymphocytes with PWM (abstract and page 175, first paragraph), quantifying the cells by cell sorting using the surface marker CD69 and further specifying and separating cells as CD4+ and/or CD8+ subpopulations (page 176, lines 6-33) via flow

cytometry using monoclonal antibodies. Lastly, the reference teaches the effects of PWM stimulation as a function of the number of cells bearing the surface marker(s) before and after stimulation (Table I). The reference makes no mention of the method within the context of diagnosis of Alzheimer's disease; however, this recitation in the preamble of the claim is non-limiting. The reference fully anticipates the active method steps required to practice the invention of claims 1-4 and 6.

14. Claims 1-6 and 8 are rejected under 35 U.S.C. 102(b) as being anticipated by Stieler et al., *NeuroReport*, 12(18): 3969-3972, published December 21, 2001, and cited as reference AF on the IDS filed 9/5/2006.

15. Instant claims 1-6 and 8 are drawn to a method of diagnosing Alzheimer's disease or an early stage of or a predisposition for this disease by means of a patient sample, the method comprising the steps of: (a) mitogenic stimulation of the cells in the sample; (b) quantification of the cells before and after stimulation by means of one or more surface markers, the cells bearing the surface markers being separated from the cells bearing no surface markers by means of antibodies directed against the surface markers; (c) determination of the stimulation index as a relationship of the number of cells bearing the surface marker before or after step (a). Dependent claims recite, wherein the cells are lymphocytes; the surface marker is CD69 and wherein the CD69+ cells are further specified with respect to CD4 and CD8; wherein the blood is stabilized by one or more anticoagulative compounds before step (a); wherein the cells are stimulated by the instantly-elected pokeweed mitogen (PWM); and wherein the

stimulation index is determined by determining protein content and/or nucleic acid content before and after stimulation.

16. The Stieler et al. reference teaches a method comprising the active steps of stimulating a citrated (“stabilized” of the claim 5) blood sample of lymphocytes with PWM (page 3969, paragraph 4), quantifying the cells by cell sorting using the surface marker CD69 and further specifying and separating cells as CD4+ and/or CD8+ subpopulations (page 3970, paragraph 1) via FACScan-analysis. Stieler et al. also teaches the effects of mitogenic stimulation as a function of the number of cells bearing the surface marker(s) before and after stimulation (Figure 1). Lastly, the reference teaches the stimulation index as a function of ApoE genotype (page 3970, paragraph 2 and Figure 3), which teaches the method further comprising a determination of the nucleic acid content (claim 8). The reference teaches the method as practiced in patients with Alzheimer’s disease with respect to “potentially diagnostic purposes” (paragraph bridging pages 3971-3972). Thus, the reference fully anticipates the active method steps required by the invention of claims 1-6 and 8 and teaches the method within the context of Alzheimer’s diagnosis.

***Claim Rejections - 35 USC § 103***

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

18. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

19. Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Stieler et al. (2001) as applied to claims 1-6 and 8 above, and further in view of Rasmussen et al., *Journal of Immunological Methods*, 146(2): 195-202, published February 5, 1992.

20. As stated above, the Stieler et al. reference teaches a method comprising the active steps of stimulating the lymphocytes of stabilized blood samples with PWM, quantifying the cells by cell sorting using the surface marker CD69 and further specifying and separating cells as CD4+ and/or CD8+ subpopulations, and determining the stimulation index as a function of the number of cells bearing the surface marker(s) before and after stimulation and further determining the stimulation index as a function of genotype. The reference teaches the method as practiced in patients with Alzheimer's disease for diagnostic purposes.

21. The Stieler reference does not teach the method wherein the antibodies in step (b) are bound to magnetic particles and the separation is carried out via immunomagnetic separation. The Rasmussen et al. reference, however, teaches that it was well-known within the art prior to the date of filing that superparamagnetic

Dynabeads® can be utilized to specify and separate lymphocyte cells that bear or do not bear the surface markers CD69, CD4 and/or CD8.

22. It would be obvious to one of ordinary skill in the art to combine the use of immunomagnetic separation, as taught by Rasmussen, with the method of Stieler. A skilled artisan would be motivated to combine because the use of Dynabeads is known in the art to confer the advantage of ease-of-use particularly within methods of cell isolation.

23. In *KSR International Co. v. Teleflex, Inc.*, the Supreme Court has stated that combining prior art elements according to known method to yield predictable results is *prima facie* obvious if the following rationale can be applied:

- (1) the prior art includes each element claimed though not necessarily in the same reference.
- (2) it was within the technical grasp of one of ordinary skill in the art to combine the elements as claimed by known methods, and that in combination, each element merely would have performed the same function as it did separately.
- (3) one of ordinary skill in the art would have recognized that the results of such combination were predictable.

(*KSR International Co. v. Teleflex, Inc.* 127 S. Ct. 1727, 82 USPQ2d 1385, Supreme Court, April 30, 2007).

24. One of ordinary skill in the art would recognize the use of immunomagnetic separation, as taught by Rasmussen, in combination with the method comprising mitogenic stimulation and quantification of cell surface markers, as taught by the Stieler prior art. A skilled artisan would be motivated to combine the prior art elements because combination would result in the same effects as reported by Stieler, but with the added advantage of ease-of-use of Dynabead technology. Based on the guidance

and direction within the prior art, such combination would have been well within the technical grasp of a skilled artisan. Since each of the elements in combination are merely performing the same function as they did separately, then one of ordinary skill in the art would have been able to predictably combine the elements with a reasonable expectation of success. Therefore, the invention as a whole is *prima facie* obvious, if not actually anticipated by the reference.

### ***Conclusion***

19. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STACEY MACFARLANE whose telephone number is (571)270-3057. The examiner can normally be reached on M,W and ALT F 7 am to 3:30, T & R 5:30 -5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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